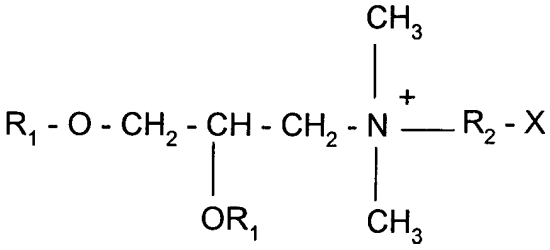
REMARKS

Reconsideration and withdrawal of the rejections of the application is respectfully requested in view of the remarks and enclosures herein.

I. THE ART REJECTIONS ARE OVERCOME

Claims 84, 85 and 118 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cox *et al.* in view of Klavinskis *et al.* Claims 84-91 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cox *et al.* in view of Klavinskis *et al.* and further in view of Xiang *et al.* and Baker *et al.* Claims 84, 92, 94, 100 and 104 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cox *et al.* in view of Klavinskis *et al.* and further in view of Li. Claims 84, 93 and 104 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cox *et al.* in view of Klavinskis *et al.* and further in view of Choi *et al.* Claims 84-95, 100-111 and 118 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cox *et al.* in view of Klavinskis *et al.* and further in view of Xiang *et al.*, Baker *et al.*, Li and Choi *et al.* These rejections will be addressed collectively and are respectfully traversed.

The present invention provides for a DNA vaccine against a bovine pathogen comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding an immunogen of the bovine pathogen, and a cationic lipid containing a quaternary ammonium salt, of the formula



in which R_1 is a saturated or unsaturated linear aliphatic radical having 12 to 18 carbon atoms, R_2 is an aliphatic radical containing 2 or 3 carbon atoms, and X a hydroxyl or amine group. The lipid can be DMRIE and the vaccine can further comprise DOPE. The vaccine can also further comprise bovine or porcine GM-CSF, or an expression vector that contains and expresses in a porcine host cell a nucleotide sequence encoding porcine GM-CSF, or an expression vector that

contains and expresses in a bovine host cell a nucleotide sequence encoding porcine GM-CSF, wherein this additional expression vector can be a plasmid.

The nucleotide sequence encoding the immunogen can have deleted therefrom a portion encoding a transmembrane domain, and the plasmid can further contain and express in a nucleotide sequence encoding a heterologous tPA signal sequence, such as a human tPA signal sequence. Even further, the plasmid can further contain a stabilizing intron, such as intron II of a rabbit beta-globin gene.

In the elected species, the bovine pathogen is bovine respiratory syncitial virus (BRSV). The immunogen can be BRSV F or BRSV G. For instance, the immunogen can be BRSV F or G, modified by substitution of the BRSV F signal sequence with a human tPA signal sequence, and/or by deletion of the transmembrane domain.

Indeed, the vaccine can comprise: (1) a first plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding bovine respiratory syncitial virus (BRSV) F, modified by substitution of the BRSV F signal sequence with a human tPA signal sequence and deletion of the transmembrane domain and contiguous C-terminal portion; and (2) a second plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding BRSV G, modified by substitution of the BRSV G signal sequence with a human tPA signal sequence and deletion of the transmembrane domain and contiguous C-terminal portion; and (3) DOPE, with the lipid being DMRIE, whereby the vaccine comprises the aforementioned two plasmids and DMRIE-DOPE.

None of the cited documents teaches or suggests an effective DNA vaccine that comprises, *inter alia*, a plasmid that expresses DNA encoding an immunogen of a pathogen affecting bovines.

The Examiner is respectfully reminded that for a Section 103 rejection to stand, there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings to arrive at the claimed invention. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the

prior art suggests the desirability of the modification." Also, the Examiner is additionally respectfully reminded that for the Section 103 rejection to be proper, **both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure**. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Furthermore, the Examiner is also respectfully reminded that MPEP 2143.01 mandates that for a Section 103 rejection, there must be some suggestion or motivation to modify reference teachings, and, that MPEP 2143.02 further mandates that for a Section 103 rejection, there must be a reasonable expectation of success.

Thus, both the case law and the MPEP require that for a Section 103 rejection, there must be some teachings, suggestion, motivation, or incentive to modify reference teachings to arrive at the claimed invention, and there must be some reasonable expectation of success of the claimed invention.

The Office Action states that the suggestion to combine the references is, in fact, present in the prior art: the references "clearly [indicate] that each of the modifications encompassed by the instant claims can be used to make a better, more efficacius immune response to a pathogen, thus resulting in a better, more efficacious vaccine." Office Action at 25-26. Further, the Office Action states that because "a bovine DNA vaccine comprising plasmids which encode and express the BRSV-F and/or BRSV-G gene" was known, it "would have been prima facie obvious to one of ordinary skill in the art [to] make all of the known modifications to the known DNA vaccine in order to make a better, more efficacious vaccine." Office Action at 26. Applicants respectfully disagree.

Of the references cited by the Examiner in making the §103 rejections, Chio *et al.*, Xiang *et al.*, Klavinskis *et al.* and Li all relate to experiments and vaccines performed in **mice**. Baker *et al.* utilizes an *in vitro* bovine bone marrow proliferation assay. Only Cox *et al.* describes *in vivo* work actually performed in **cattle**. However, Cox et al. is directed only towards a vaccine for a bovine pathogen comprising a plasmid which contains and expresses a nucleic acid molecule having sequences encoding a pathogenic polypeptide.

In fact, Cox *et al.* first performed experiments in mice, and later in cattle, in order to verify whether the previous findings could be applied to cattle. In other words, there was no guarantee that the findings in mice could be extrapolated to cattle.

And, none of the other cited references contain any teaching or suggestion that the experiments described therein could be extrapolated into bovines with any expectation of success.

The Examiner's attention is respectfully drawn to Schultz *et al.* (Intervirology, 2000, 43:197-217), submitted previously, additional copy provided herewith. Schultz provides a review of antiviral DNA vaccine research from 1998-2000. One conclusion drawn by Schultz *et al.* exemplifies why vaccine results may not be extrapolated between species, and particularly why teachings or suggestions as to mice cannot be extrapolated to larger animals such as bovines or porcines:

> Several DNA vaccines have proven efficacious in small animal models, especially mouse models. In larger species, DNA vaccines were less effective.
> Schultz at 203.

Thus, contrary to the assertions in the Office Action, one cannot extrapolate vaccine data from smaller animals such as mice to larger animals such as bovines.

Therefore, Cox *et al.*, either individually or in any combination, cannot be said to teach or suggest the instant invention. Further, according to the conclusions of Schultz *et al.*, there is no reasonable expectation that the jump from mice to bovines, would be successful.

It is alleged Klavinskis *et al.* remedies the failures of Cox *et al.* by teaching a plasmid DNA vaccine complexed with DMRIE/DOPE. Applicants disagree. Klavinskis *et al.* relates to intranasal vaccination of mice against sexually transmitted diseases. One of skill in the art would have no motivation to combine Klavinskis et al. with Cox et al., nor would one of skill in the art have any expectation of success in doing so.

Accordingly, Cox and Klavinskis fail to teach or suggest the instant invention, and reconsideration and withdrawal of the Section 103 rejection based on Cox and Klavinskis are respectfully requested.

As discussed above, the results of Xiang *et al.* in mice cannot be extrapolated to bovines such that Xiang does not remedy the deficiencies of Cox and Klavinskis as alleged in the Office Action. And, Baker *et al.* deals only with DNA encoding bovine GM-CSF. Nowhere in Baker is there any teaching or suggestion that GM-CSF protein could or should be administered as a component of a DNA vaccine or be co-expressed in a DNA vaccine, let alone a vaccine comprising a DNA plasmid and a cationic lipid, as in the instant claims. In fact, Baker does not

discuss vaccines in any form. Thus, Baker fails to remedy the deficiencies of Cox, Klavinskis and Xiang.

Therefore, the combination of Cox, Klavinskis, Xiang and Baker does not result in the claimed invention, as this combination does not teach or suggest the instant invention, nor does it offer any expectation that the present invention would be successful. Further, it is respectfully submitted, the combination fails to even raise to the standard of "obvious to try" (which, as mentioned earlier, is NOT the standard for making a Section 103 rejection). Accordingly, Cox, Klavinskis, Xiang and Baker, either individually or in any combination, fails to teach or suggest the instant invention. Therefore, reconsideration and withdrawal of the Section 103 rejection based on this combination are respectfully requested.

As discussed above, the combination of Cox *et al.* and Klavinskis *et al.* does not teach or suggest the instant invention. The combination of these documents does not provide or even suggest an efficacious DNA plasmid vaccine expressing DNA encoding an immunogen of a pathogen affecting bovines, and also comprising a cationic lipid. Li *et al.* does not cure this defect.

Li involves plasmids expressing RSV F that were tested in mice. Li is no better than Xiang; and, in view of Schultz, submitted herewith, fails to provide teachings or suggestions as to the instant invention or supply the deficiencies of Cox *et al.* and Klavinskis *et al.* Accordingly, Cox *et al.*, Klavinskis *et al.* and Li *et al.*, either individually or in any combination, fail to teach or suggest the instant invention.

As discussed above, the combination of Cox *et al.* and Klavinskis *et al.* does not teach or suggest the instant invention. Just as Li fails to cure these deficiencies, likewise, that Choi may relate to human tPA fails to remedy the deficiencies of Cox *et al.* and Klavinskis *et al.* For instance, Choi also only involved tests with mice, such that Choi is no better than Xiang or Li; and, in view of Schultz submitted herewith, fails to provide teachings or suggestions as to the instant invention. Further still, Choi does not teach or suggest a human tPA/BRSV F or G fusion expressed *in vivo* in a bovine host by a DNA plasmid vaccine containing a cationic lipid, or the benefits thereof. Accordingly, Cox *et al.*, Klavinskis *et al.* and Choi *et al.* either individually or in any combination, fails to teach or suggest the instant invention.

Additionally, the combination of Cox *et al.* with all of the above mentioned documents, i.e. Cox *et al.* in combination with Klavinskis *et al.*, Xiang *et al.*, Baker *et al.*, Li and Chio *et al.* fails to teach or suggest the instant invention.

As discussed above, there is no teaching or suggestion present in any of the references which would encourage one of skill in the art to combine the references in order to arrive at the present invention. Cox *et al.*, Klavinskis *et al.*, Xiang *et al.*, Baker *et al.*, Li and Chio *et al* are primarily concerned with mice. There is no teaching or suggestion that such findings may be extrapolated to larger animals, including bovines. Furthermore, these references are so dissimilar that one would not be motivated to combine them. For instance, Choi *et al.* relates to vaccination using PowderJet particle delivery, while Klavinskis relates to intranasal immunization. One of skill in the art would have no motivation to combine two references that are focused on two different, specific methods of vaccination. Consequently, the combination of Cox *et al.* with all of the above mentioned documents, i.e. Cox *et al.* in combination with Klavinskis *et al.*, Xiang *et al.*, Baker *et al.*, Li and Chio *et al.* fails to teach or suggest the instant invention

Therefore, reconsideration and withdrawal of the Section 103 rejections based upon the combinations of: Cox *et al.* in view of Klavinskis *et al,* Cox *et al.* in view of Klavinskis *et al.* and further in view of Xiang *et al.* and Baker *et al.*, Cox *et al.* in view of Klavinskis *et al.* and further in view of Li, Cox *et al.* in view of Klavinskis *et al.* and further in view of Choi *et al,* Cox *et al.* in view of Klavinskis *et al.* and further in view of Xiang *et al.*, Baker *et al.*, Li and Choi *et al.*, are respectfully requested.

II. THE DOUBLE PATENTING REJECTIONS ARE OVERCOME

Claims 84-114 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 4, 5 and 16-19 of co-pending application Serial No .09/766,442. Claims 84, 85, 96, 112 and 116-118 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 (Audonnet) in view of Klavinskis *et al.* Claims 84-91 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims5-8 of U.S. Patent No. 6,376,473 in view of Klavinskis *et al.* and further in view of Xiang *et al.* and Baker *et al.*

Claims 84, 92, 94, 95, 100 and 108 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 in view of Klavinskis *et al.* and further in view of Li. Claims 84, 93, 97, 98 and 104 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 in view of Klavinskis *et al.* and further in view of Choi *et al.* Claims 84-118 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 in view of Klavinskis *et al.*, and further in view of Xiang *et al.*, Baker *et al.*, Li and Choi *et al.* The rejections are traversed and will be addressed collectively.

Regarding the provisional double patenting rejection over co-pending application Serial No .09/766,442, it is respectfully requested that this rejection be withdrawn in the present application and issued in U.S.S.N. 09/766,442 after allowance of the present application.

Regarding the remaining rejections, as discussed previously, there is no motivation to combine any of the above documents, and a combination of such documents does not cure the deficiencies of Audonnet or render obvious the present invention.

Accordingly, it is respectfully submitted that the double patenting rejections cannot stand; reconsideration and withdrawal of the rejections is respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview, with supervisory review, is respectfully requested prior to issuance of any paper other than a Notice of Allowance. The Examiner is additionally respectfully requested to telephonically contact the undersigned to arrange a mutually convenient time and manner for the interview. The Examiner is also invited to telephonically contact the undersigned if there are any minor, formal issues that need resolving prior to issuance of a Notice of Allowance, with a view towards resolving such minor, formal issues via telephonic interview.

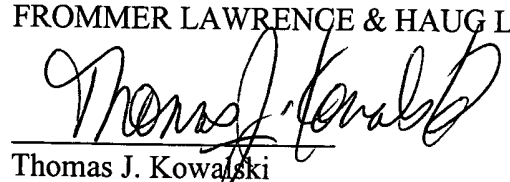
CONCLUSION

In view of these amendments, remarks and article and attachments submitted herewith, the application is in condition for allowance. Early and favorable reconsideration of the

application, reconsideration and withdrawal of the rejections, and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By: 

Thomas J. Kowalski
Reg. No. 32,147
Tel 212-588-0800
Fax 212-588-0500